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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/070,480	07/08/2002	Takahisa Nakai	12178/2	4713
26646	7590	01/26/2006	EXAMINER	
KENYON & KENYON LLP ONE BROADWAY NEW YORK, NY 10004			STEADMAN, DAVID J	
			ART UNIT	PAPER NUMBER
			1656	
DATE MAILED: 01/26/2006				

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/070,480	Applicant(s) NAKAI ET AL.	
	Examiner David J. Steadman	Art Unit 1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 November 2005 and 09 November 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-3 and 5-39 is/are pending in the application.
- 4a) Of the above claim(s) 2,3 and 8-35 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,5-7 and 36-39 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 28 February 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>11/4/05</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Application Status

1. Claims 1-3 and 5-39 are pending in the application.
2. Applicant's amendments to the claims, filed on 11/4/2005 and 11/9/2005, are acknowledged. The claim listing filed on 11/9/2005 replaces all prior versions and listings of the claims.
3. Applicant's amendments to the abstract and the specification, filed on 11/4/2005, are acknowledged. Regarding the amendment to the title of the specification, applicant is reminded that such amendment should comply with the requirements of 37 CFR 1.121 by showing strikethrough and underline relative to the previous version.
4. Receipt of an information disclosure statement (IDS), filed on 11/4/2005, is acknowledged.
5. Applicant's arguments filed on 11/4/2005 in response to the Office action mailed on 8/4/2005 have been fully considered and are deemed to be persuasive to overcome some of the objections and/or rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.
6. The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Election/Restriction

7. Applicant's election of Group II, claims 1 and 4-7, in the reply filed on 5/20/2005 is acknowledged. Because applicant did not distinctly and specifically point out the

supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

8. Claims 2-3 and 8-35 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 5/20/2005.

9. Claims 1, 5-7, and 36-39 are being examined on the merits.

Information Disclosure Statement

10. The reference cited in the IDS filed on 11/4/2005 has been considered by the examiner. A copy of Form PTO-1449 is attached to the instant Office action.

Objections to the Specification

11. The attempt to incorporate subject matter into this application by reference to a hyperlink embedded in the specification (for example, page 4, line 20) is improper. Incorporation of subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP 608.01 regarding hyperlinks in the specification and 608.01(p), paragraph I regarding incorporation by reference.

Claim Objections

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12. Claims 1, 5-7, and 36-39 are objected to as being grammatically incorrect. It is suggested that applicant insert "A" at the beginning of claims 1, 7, 36, and 39 and insert "The" at the beginning of claims 5-6 and 37-38.

Claim Rejections - 35 USC § 112, First Paragraph

13. Claims 36-39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

MPEP § 2163 states, "when filing an amendment an applicant should show support in the original disclosure for new or amended claims" and "[i]f the originally filed disclosure does not provide support for each claim limitation, or if an element which applicant describes as essential or critical is not claimed, a new or amended claim must be rejected under 35 U.S.C. 112, para. 1, as lacking adequate written description".

As support for newly added claim 36 (claim(s) 37-39 dependent therefrom), applicant cites claim 8 (see p. 11, third full paragraph of the instant response). However, it is noted that the limitations of claim 8 do not support newly added claim 36. For example, claim 8 recites a specific concentration of PEG or PEGMME, which is not present in claim 36. In this case, claim 36 is unlimited with respect to the concentration of PEG or PEGMME. Claim 8 is also limited with respect to the pH of the buffering

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agent. However, claim 36 is unlimited in this regard. As such, claim 8 fails to support newly added claim 36.

Applicant is invited to show support for newly added claim 36.

14. Claims 36-39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claim 36 (claim(s) 37-39 dependent therefrom) is drawn to a decarbamylase crystal of SEQ ID NO:2 having space group $P2_12_12_1$ prepared by the recited method.

The Court of Appeals for the Federal Circuit has held that a “written description of an invention involving a chemical genus, like a description of a chemical species, ‘requires a precise definition, such as by structure, formula [or] chemical name,’ of the claimed subject matter sufficient to distinguish it from other materials.” UC California v. Eli Lilly, (43 USPQ2d 1398). For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. MPEP § 2163 states that a representative number of

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species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. At the time of the invention, it was well-known in the art that the structure of a protein crystal was defined by three repeating vectors a , b , and c , with angles α , β , and γ , between them. See pp. 586 and 2725 of the "Encyclopedia of Molecular Biology" (Creighton, T., John Wiley and Sons, Inc. New York, 1999).

The specification discloses only a single species of the genus of claimed crystals, *i.e.*, a crystal of unliganded SEQ ID NO:2 having the space group $P2_12_12_1$ and the unit cell dimensions $a=81.5-82.5 \text{ \AA}$, $b=133.0-135.0 \text{ \AA}$, and $c=119.5-121.5 \text{ \AA}$ (specification at p. 6). It is known in the prior art that a crystal having space group $P2_12_12_1$ has angles $\alpha=\beta=\gamma=90^\circ$. Other than this single species, the specification fails to disclose any other representative species of the claimed genus of crystals, which encompasses widely variant crystals having any unit cell dimensions prepared under any precipitant solution containing PEG or PEGME and any buffering agent, allowing the resultant mixture to stand for any time until a crystal forms. While MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus," it also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus." The unit cell dimensions of the genus of crystals is undefined and thus, encompass widely variant species.

Given the lack of description of a representative number of protein crystals, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

15. The enablement rejection of claims 1 and 5-7 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in the prior Office action (see ¶11 at pp. 7-9 of the 8/4/2005 Office action). New claims 36-39 are included in the rejection. Thus, claims 1, 5-7, and 36-39 are rejected.

RESPONSE TO ARGUMENT: Applicant argues that based on the disclosed working example for making crystals of SEQ ID NO:1, a skilled artisan could “easily predict how to make crystals of SEQ ID NO:2.” Applicant argues SEQ ID NO:1 and 2 are 99.1% identical, having only three amino acid variations – H57Y, P203E, and V236A. Applicant further argues SEQ ID NO:1 and 2 have substantially the same secondary structure by virtue of their related amino acid sequences, particularly as the amino acid variations do not occur within the alpha-helix or beta-sheet structural units of the wild-type decarbamylase. According to applicant, undue experimentation is not required to make the claimed crystals.

Applicant's argument is not found persuasive. Applicant does not dispute that the crystallization conditions for the claimed crystal are not disclosed in the specification. What is disputed is whether the working example crystallization conditions for SEQ ID

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NO:1 can be used for crystallization of SEQ ID NO:2, thus generating a diffraction-quality crystal having the recited space group and unit cell dimensions.

According to applicant, the two proteins differ at only 3 out of 303 amino acids. However, it is noted that the substitutions significantly change the local volume, charge, and/or hydrophobicity. This is evidenced by the specification, which discloses that “the mutation from proline to glutamic acid [at position 203] allows the carboxyl group of the side chain of the glutamic acid to form an ionic or hydrogen bond with the guanidine group of the side chain of arginine at position 139” (p. 53, lines 25-29), *i.e.*, the mutation at position 203 potentially introduces a new salt bridge linking E203 and R139, which could prevent conformational flexibility of the molecule that may be required for crystallization. Also, while none of the mutations may alter the alpha-helical or beta-sheet structures of the polypeptide, it is highly unpredictable as to whether the tertiary structure of the protein is affected by the mutations and whether or not the packing of the protein molecules within the resulting crystal would be altered. In this case, without empirically determining whether the same crystallization conditions that achieve diffraction-quality crystallization of first protein will also achieve diffraction quality crystallization of a second protein, there is no way to know *a priori* those conditions that will lead to the successful crystallization of a diffraction-quality protein crystal as evidenced by the prior art. For example, Kierzek et al. (*Biophys Chem* 91:1-20) teaches that “the major obstacle...to study protein structures by means of crystallography is protein crystallization” (p. 2, left column, top). Kierzek et al. teaches the reason that protein crystallization is such a formidable obstacle is that “each protein crystallizes

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under a unique set of conditions that cannot be predicted from easily measurable physico-chemical properties” and that “crystallization conditions must be empirically established for each protein to be crystallized” (underline added for emphasis, p. 2, left column, top). Thus, it is clear from the teachings of the prior art that one cannot predict those conditions that are suitable for obtaining a diffraction-quality crystal based on the crystallization conditions of a related protein. While one can argue that instead of predicting those crystallization conditions, one can apply the same conditions for crystallization of SEQ ID NO:1 as disclosed at p. 46 of the specification to the crystallization of SEQ ID NO:2. However, it is highly unpredictable as to whether these crystallization conditions will result in a crystal having the required space group and/or unit cell dimensions and/or will be of diffraction quality.

At least for the reasons of record and the reasons stated above, the specification fails to enable a skilled artisan to make the claimed crystals.

Conclusion

16. Status of the claims:

Claims 1-3 and 5-39 are pending.

Claims 2-3 and 8-35 are withdrawn from consideration.

Claims 1, 5-7, and 36-39 are rejected.

No claim is in condition for allowance.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Thurs and alternate Fri, 7:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



David J. Steadman, Ph.D.
Primary Examiner
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